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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/966,803	09/27/2001	Jay Short	DIVER1130-8	3294

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EXAMINER
RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,803	SHORT ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-92* is/are pending in the application.

4a) Of the above claim(s) *1-41 and 56-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-92 are pending.

It is noted that the examination of the instant application has been assigned to a different Examiner in Group Art Unit 1652.

Applicant's election without traverse of Group IV, claims 42-55, drawn to a method of generating a variant, in Paper No. 14, filed on 6/20/2003 is acknowledged.

Claims 1-41 and 56-92 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

1. The use of the trademarks has been noted in this application. See for example, "PHARMACIA", "PROMEGA", etc. in page 51, paragraph 165. They should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Method of generating variants of a *Thermococcus* enzyme having amidase activity".

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/609,570 filed on 06/30/2000, 09/427,372 filed on 10/25/1999, 09/261,006 filed on 03/02/1999, and 08/664,646 filed on 06/17/1996.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on 9/27/2001 (Paper No. 7) and 11/6/2002 (Paper No. 12) are acknowledged. The reference listed as "W70508" in the IDS submitted on 11/6/2002 is not in conformance with MPEP § 609 and has not been considered for the following reasons. No date has been provided for this reference and no copy has been submitted. It is suggested that if the reference is a specific sequence disclosed in a publicly available database, such reference be cited by its accession number and date of public availability.

Drawings

5. The drawings have been reviewed and are objected under 37 CFR 1.84 or 1.152. See attached Notice of Draftsperson's Patent Drawing Review. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDOMENT of the application. In addition, if amendments to the specification are needed due to drawing corrections, Applicant is requested to submit such amendments while the case is being prosecuted to expedite the processing of the application.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 42-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 42 (claims 43-55 dependent thereon) is indefinite in the recitation of "variant" for the following reasons. The term "variant" has been defined in the specification (page 13, paragraph 52) as "polynucleotide or polypeptide modified at one or more base pairs, codons, introns, exons, or amino acid residues yet still retain the biological activity of an amidase". However, this definition of "variant" is contrary to the accepted meaning of the term since in general, a variant of a polypeptide/polynucleotide may or may not maintain the function of the polypeptide/polynucleotide from which it derives. Furthermore, the specification (page 5, paragraph 23) also uses the term "variant" in reference to a polypeptide which may not have the enzymatic function of the polypeptide of SEQ ID NO: 2. For examination purposes, the definition given in the specification, paragraph 52, will be used. Correction is required.

9. Claim 42 (claims 43-55 dependent thereon) is indefinite in the recitation of "obtaining a nucleic acid comprising a sequence as set forth in SEQ ID NO: 1, sequences substantially identical thereto, sequences complementary thereto, fragments comprising at least 30 consecutive nucleotides thereof, and fragments comprising at least 30 consecutive nucleotides of the sequences complementary to SEQ ID NO: 1" for the following reasons.

First, as written, it is unclear if the method comprises obtaining a nucleic acid having the sequences as recited and the fragments as recited or if the method comprises obtaining either the nucleic acid or the fragments as recited.

Furthermore, the claim is indefinite in the recitation of "sequences complementary thereto" as it is unclear if the term "thereto" refers to SEQ ID NO: 1 or "the substantially identical" sequence. The term "complementary" is also indefinite since it is unclear which "complementary sequences" are encompassed by the claims. A complementary sequence can refer to a sequence which is fully or partially complementary to another. Applicants have not define the term "complementary", as it relates to size, in the specification either. If applicants wish to claim the entire complementary sequence, it is suggested that the term "complementary" be replaced with "completely complementary".

The claim is also indefinite in the recitation of "fragments comprising...thereof" as it is unclear which nucleic acids are being referred to by the term "thereof". Since the term "substantially identical" in regard to nucleic acid sequences has been defined in the specification (page 11, paragraph 47), the term will be interpreted as "sequences that have at least 50% identity over a region of any size". For examination purposes, the claim will be interpreted as being drawn to a method of generating a variant comprising obtaining a nucleic acid selected from the group consisting of (a) the polynucleotide of SEQ ID NO: 1, (b) any polynucleotide having at least 50% sequence identity to any fragment of the polynucleotide of SEQ ID NO: 1, (c) any polynucleotide which is completely complementary to (a) or (b), (d) a fragment of at least 30 consecutive nucleotides of (a), (b), or (c). Correction is required.

10. Claim 42 (claims 43-55 dependent thereon) is indefinite in the recitation of "modifying one or more nucleotides in said sequence ....., deleting one or more nucleotides in said sequence, or adding....to said sequence" for the following reasons. Deletion, addition and/or modification as recited in the claim refers to a nucleic acid and not to a sequence. As known in the art, sequences are just graphical representations of the order in which nucleotides are assembled in a nucleic acid. Therefore, it is suggested that the claim be amended to recite "substituting one or more nucleotides in said nucleic acid to another nucleotide, deleting one or more nucleotides in said nucleic acid, or adding one or more nucleotides to said nucleic acid". For examination purposes, the suggested language will be used. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 42-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn in part to a method for generating a variant comprising obtaining (1) a genus of nucleic acids of <u>any function</u> having at least 50% sequence identity to any fragment of the polynucleotide of SEQ ID NO: 1, (2) a genus of nucleic acids which are

completely complementary to (1), (3) a genus of nucleic acid fragments of at least 30 consecutive nucleotides of (1), (2), or (3). While the specification discloses the polynucleotide of SEQ ID NO: 1 and the corresponding polypeptide, as well as a method for generating polynucleotide/polypeptide variants of the polynucleotide/polypeptide of SEQ ID NO: 1 or 2 which still retain amidase activity (page 13, paragraph 52), the specification fails to disclose a method of creating variants, as defined in the specification, using (1) nucleic acids of any function having at least 50% sequence identity to any fragment of the polynucleotide of SEQ ID NO: 1 or (2) nucleic acids which are fragments of (1). It is noted that the term "variant" has been defined in the specification (page 13, paragraph 52) as "polynucleotide or polypeptide modified at one or more base pairs, codons, introns, exons, or amino acid residues yet still retain the biological activity of an amidase". The specification does not disclose the critical structural elements required in a nucleic acid having at least 50% sequence identity to any fragment of the polynucleotide of SEQ ID NO: 1 to encode a polypeptide which has amidase activity, nor does it describe which fragments of such nucleic acid would encode a polypeptide having amidase activity.

While one could argue that the nucleic acids required to practice the claimed method are adequately described since one can isolate nucleic acids of similar function by sequence comparison using the polynucleotides/polypeptides of the instant application or the prior art, the state of the art teaches that sequence comparison alone should not be used to determine function and that small structural changes can drastically change function. Bork (Genome Research, 10:398-400, 2000; cited in the IDS) teaches protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Witkowski et al. (Biochemistry

38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995; cited in the IDS) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998; cited in the IDS) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a single species of the genera of nucleic acids required to practice the invention which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of the claimed method. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

13. Claims 42-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for generating variants comprising obtaining a nucleic acid comprising the polynucleotide of SEQ ID NO: 1 and modify such nucleic acid as encompassed by the claims, does not reasonably provide enablement for a method of generating variants comprising obtaining <u>any</u> nucleic acid which is at least 50% sequence identical to any fragment of the polynucleotide of SEQ ID NO: 1 and modify such nucleic acid according to the claims. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims as described above is not commensurate with the enablement provides in regard to the large number of unknown polynucleotides required to practice the claimed method. As indicated above, the specification describes a method of generating variants of the polynucleotide/polypeptide of SEQ ID NO: 1 or 2 which still retain amidase activity (page 13, paragraph 52), but the specification fails to disclose a method of creating variants, as defined in the specification, using (1) nucleic acids of any function having at least 50% sequence identity to any fragment of the polynucleotide of SEQ ID NO: 1 or (2) nucleic acids which are fragments of (1). Since the variant obtained by the method as described in the specification still retains amidase activity, it is unclear how one of skill in the art can practice the claimed method with polynucleotides of any function as described above. In addition, the specification does not disclose the critical structural elements required in any nucleic acid to encode a polypeptide which has amidase activity, nor does it describe which fragments of such nucleic acid would encode a polypeptide having amidase activity. Furthermore, as discussed above, the state of the art teaches that isolation of polynucleotides of similar function is unpredictable, as evidenced by Bork, Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. Since structure

determines function, one of skill in the art would require some knowledge or guidance as to how structure correlates with function to isolate the polynucleotides required to practice the claimed method. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to maintain the desired function, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to screen and isolate those polynucleotides, as encompassed by the claims, which encode polypeptides of amidase activity, to practice the claimed method. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Conclusion

14. No claim is in condition for allowance.

15. It is noted that if the references cited by the Examiner are too long, only relevant pages will be enclosed with the instant Action.

16. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

17. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
August 3, 2003

REBECCA E. PRUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600